Synthesis of Functionalized Alkenes by a Transition-Metal-Free Zweifel Coupling

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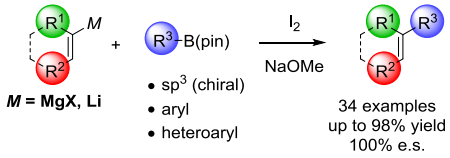
Supporting Information Placeholder



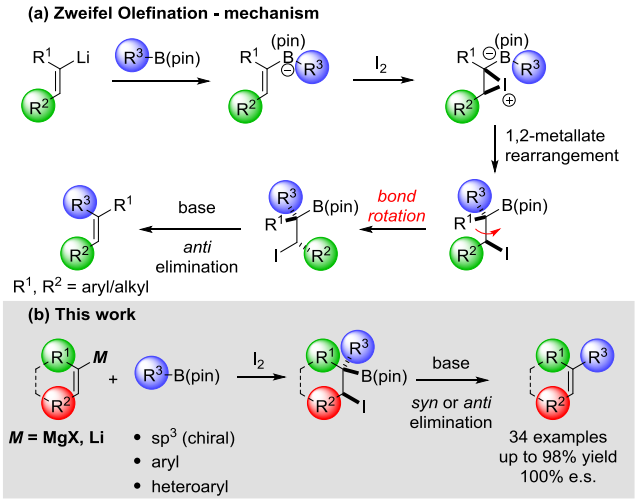
ABSTRACT: The Zweifel reaction is a powerful method for the synthesis of alkenes, serving as a transition-metal-free alternative to the Suzuki–Miyaura reaction. To date, the scope of the Zweifel coupling has been rather narrow, and has focused mainly on the coupling of vinyl lithium reagents to synthesize simple aryl- and alkyl-substituted olefins. Herein, the development of a general transition-metal-free coupling process enabling the coupling of Grignard reagents or organolithiums is described. This method enables the enantiospecific synthesis of a wide variety of functionalized acyclic and cyclic olefin products.

The geometrically controlled synthesis of functionalized alkenes continues to receive prominent attention due to their prevalence in pharmaceuticals, natural products and materials.[1] The Suzuki–Miyaura cross-coupling reaction constitutes an extremely versatile and convergent method for the assembly of alkenes.[2] However, although the coupling of vinyl halides with primary and sp^2-boronate partners takes place with high efficiency, the corresponding reactions with secondary and tertiary (chiral) boronic esters do not.[3] Furthermore, the high cost and toxicity of the palladium complexes that are typically employed as catalysts in such coupling processes impact on its attractiveness.[4]

We have recently become interested in the Zweifel olefination,[5] which represents a transition-metal-free alternative to the Suzuki–Miyaura coupling. In this process, a vinyl metal species is combined with a boronic ester resulting in the formation of a boronate complex (Scheme 1). Treatment of this intermediate with iodine results in the formation of an iodonium ion, which is poised to undergo a stereospecific 1,2-metallate rearrangement affording a β-iodoboronic ester. Upon addition of a base, this intermediate undergoes *anti* elimination, resulting in the formation of the corresponding alkene.[6] Although there have been several elegant reports detailing the development of the Zweifel coupling, to date the method has principally been applied to the coupling of simple alkyl- and aryl-substituted acyclic vinyl lithiums. Moreover, the introduction of an unsubstituted vinyl moiety requires the use of vinyl lithium, which is typically prepared *in situ* from highly toxic tetravinyltin.[7] As a consequence, the Zweifel reaction has not been widely utilized and has only been employed in a handful of synthetic applications.[8]

Our aim at the outset of this work was to extend the utility of the Zweifel olefination by developing a practical method enabling the coupling of simple vinyl Grignard reagents with boronic esters. Unlike the corresponding vinyl lithium reagents, solutions of vinyl Grignard reagents are commercially available and bench stable.[9]

Scheme 1. Zweifel Olefination

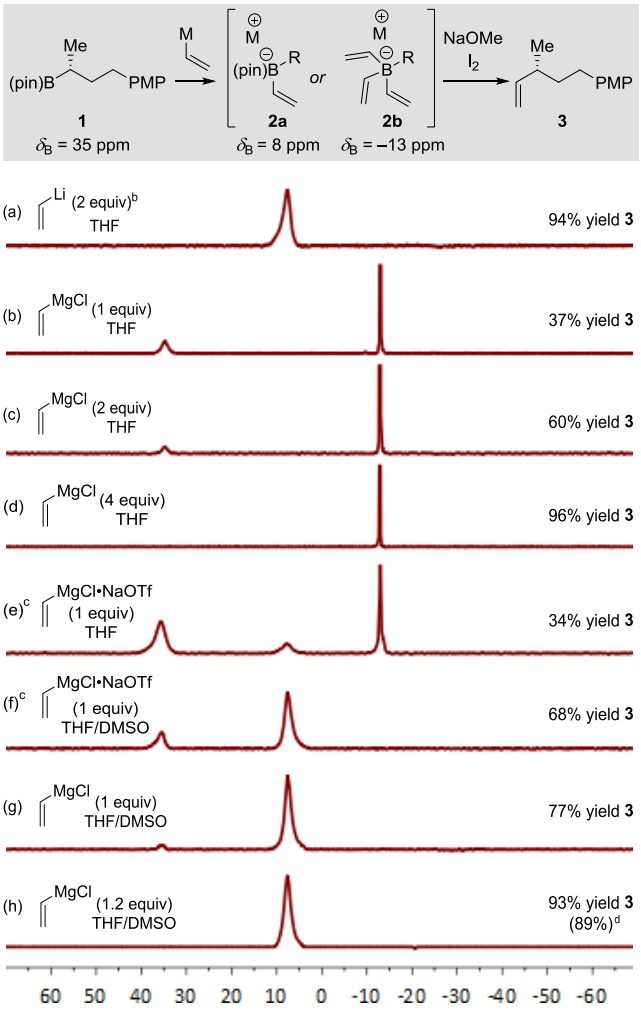


We also hoped to extend the scope of the coupling process to encompass densely functionalized, cyclic vinyl metals. The coupling of cyclic vinyl metals is of particular interest, because the cyclic β-iodoboronic ester intermediates cannot undergo bond rotation to achieve an *anti* relationship between boronic ester and iodide. Instead a challenging *syn* elimination is required to obtain the cycloalkene products.[10]

We commenced our study with an investigation of the introduction of an unsubstituted vinyl group. A typical reference coupling between boronic ester **1** and vinyl lithium (prepared *in situ* from tetravinyl stannane) provided the desired product **3** in 94% yield (Scheme 2, entry a).[7b] However, unfortunately when we attempted to carry out Zweifel coupling of boronic

ester **1** with an equimolar quantity of vinylmagnesium chloride, the product **3** was formed in only 37% yield (entry b).

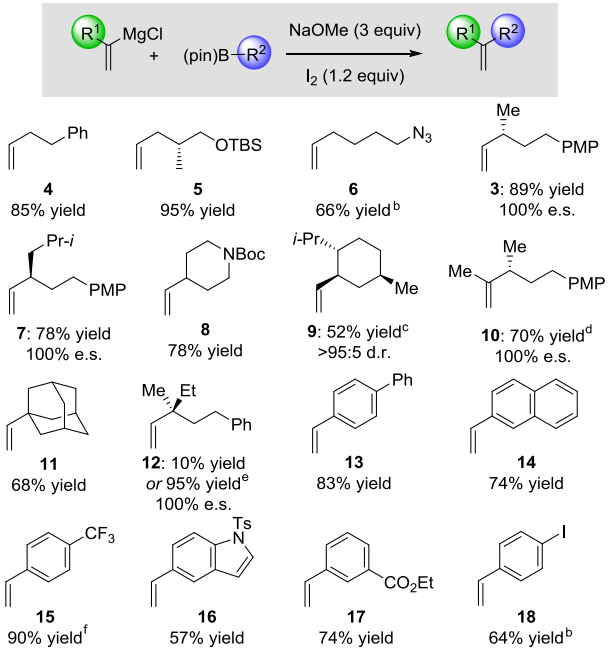
Scheme 2. Zweifel coupling with vinyl Grignard: reaction optimization via ^{11}B NMR analysis.[a]



[a] Reaction conditions: **1** (1 equiv), vinyl metal (1–4 equiv); then NaOMe (3–8 equiv), I_2 (1.2–4 equiv). The scheme shows ^{11}B NMR spectra recorded in non-deuterated reaction solvents prior to addition of I_2/NaOMe. Yields of **3** were determined by ^{1}H NMR analysis *vs* 1,1,2,2-tetrachloroethane as an internal standard. [b] Vinyllithium was generated from tetravinyltin (1 equiv) and *n*-butyllithium (1.6 M in hexanes, 2 equiv). [c] Vinyl-MgCl (1.6 M in THF, 1 equiv), NaOTf (2 equiv). [d] Yield of isolated product **3** after column chromatography on silica gel.

We suspected that boronate complex formation was the problematic step in this sequence, and accordingly we analyzed the intermediate by ^{11}B NMR spectroscopy. Instead of the usual peak expected for boronate complex **2a** at 8 ppm (for example that observed with vinyl lithium, entry a), we observed a mixture of unreacted boronic ester **1** (35 ppm) along with a new sharp singlet at –13 ppm (entry b). This is consistent with the formation of trivinyl boronate complex **2b** in which the pinacol ligand has been displaced by three equivalents of vinylmagnesium chloride. In line with our previous studies in this area,[11] we found that addition of excess vinyl magnesium chloride (2 or 4 equiv) resulted in increased conversion of the starting boronic ester to **2b** and the desired boronate complex **2a** was not observed (entries c-d). Although addition of iodine and methanol provided the coupled product **3** in good yield, this approach is non-ideal for reasons of both economy and functional-group compatibility. Morken and co-workers have very recently reported an elegant strategy for palladium-catalyzed conjunctive cross-coupling of vinyl Grignards, in which it was observed that boronate complex formation could be promoted by addition of alkali metal triflates and introduction of DMSO as a co-solvent.[12] We found that upon addition of sodium triflate (see SI for full details of optimization) a small amount of the desired boronate complex **2a** was observed (8 ppm) although a significant quantity of **2b** was also formed (entry e). We were pleased to find that performing the reaction with NaOTf in 1:1 DMSO/THF completely suppressed formation of **2b** and following addition of I_2 and NaOMe, **3** was obtained in a promising 68% yield (entry f). For Morken, sodium triflate plays a key role in subsequent chemistry as a halide scavenger, but we speculated that it might not be required in our case. Pleasingly, we found that carrying out the reaction in the absence of NaOTf in 1:1 THF/DMSO we observed high conversion to the desired boronate complex **2a** (entry g). By adding a slight excess (1.2 equiv) of vinyl magnesium chloride, complete conversion to **2a** was observed, and after addition of I_2 and NaOMe, the coupled product **3** was isolated in 89% yield (entry h).

Scheme 3. Coupling of Grignard reagents with boronic esters: substrate scope[a]



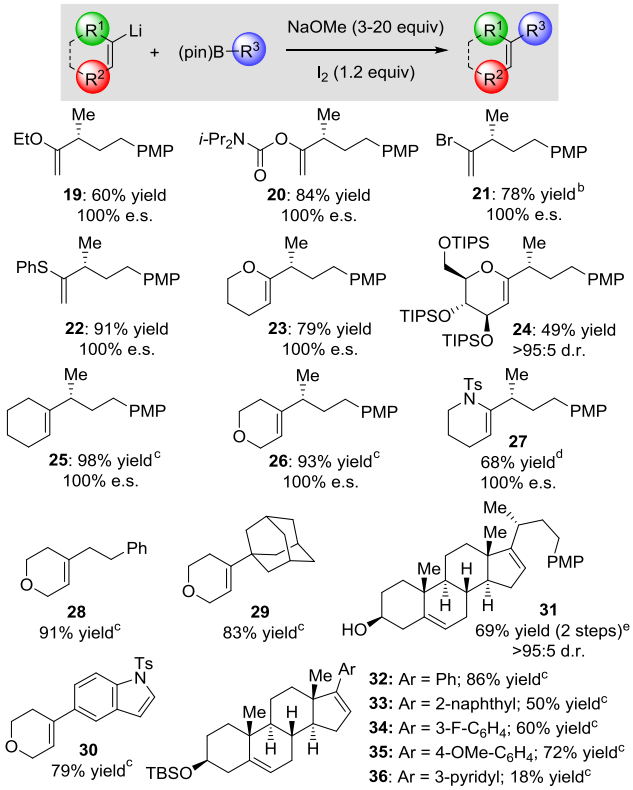
[a] Reaction conditions: boronic ester (1 equiv), vinylmagnesium chloride (1.6 M in THF, 1.2 equiv), 1:1 THF/DMSO, 0 °C to rt, 30 min; then NaOMe (3 equiv), I_2 (1.2 equiv), THF/DMSO/MeOH, 0 °C, 30 min. [b] ^{1}H NMR yield *vs* 1,1,2,2-tetrachloroethane. [c] With vinylmagnesium chloride (1.6 M in THF, 2 equiv). [d] With isopropenylmagnesium bromide (0.5 M in THF, 2 equiv). [e] With 4 equiv vinyl-MgCl without DMSO. [f] ^{19}F NMR yield *vs* hexafluorobenzene.

Employing these optimized conditions we evaluated the generality of the process (Scheme 3). Primary boronic esters underwent the desired coupling process affording **4**–**6** in excellent yields. Secondary boronic esters could also be successfully employed as starting materials, providing products **7**–**9** in good yield with complete stereospecificty. Notably, the mild nature of Grignard reagents enables chemoselective coupling to occur in the presence of functional groups such as azides (**6**) and carbamates (**8**).[13] It was also possible to employ a Grignard reagent bearing an α-methyl substituent to obtain **10** in 70% yield. Our optimized conditions also enabled the successful coupling of an unhindered tertiary boronic ester to form **11**; however, for acyclic tertiary boronic esters, the products (e.g. **12**) were obtained in reduced yield. We found that an effective solution to this problem was to add four equivalents of vinyl magnesium chloride in THF (*c.f.* Scheme 2, entry d) and using this method, **12** was obtained in 95% yield. Finally, we carried out coupling reactions between vinyl magnesium chloride and a series of aromatic boronic esters. Using this method, a range of electron-rich, electron-deficient and heteroaryl groups could be introduced including boronic esters containing reactive functional groups such as vinyl iodides and ethyl esters. The latter example is especially noteworthy, since ethyl esters are not compatible with the more reactive vinyl lithium reagents.

Next we turned our attention to carrying out Zweifel reactions with more complex, substituted vinyl partners (Scheme 4). Employing conditions recently reported by our group, we were able to synthesize vinyl ether **19** (60% yield, 100% e.s.), vinyl carbamate **20** (84% yield, 100% e.s.) and vinyl bromide **21** (78% yield, 100% e.s.).[11,14] We found that the process could also be extended to the coupling of a lithiated vinyl sulfide, providing **22** in 91% yield with complete enantiospecificity. We next examined the coupling of lithiated dihydropyran to give **23**. Interestingly, we found that in the absence of base, the intermediate β-iodoboronic ester could be isolated (see SI for details), implying that the *syn* elimination process is indeed slow compared with acyclic examples. Fortunately our standard elimination conditions (3 equiv NaOMe, 30 min, 0 °C) were able to promote the desired *syn* elimination, affording the coupled product **23** in 79% yield with complete enantiospecificity. The methodology could also be employed in a more complex setting – glycal derivative **24** was obtained in 49% yield as a single diastereoisomer. We next attempted to extend the process to the coupling of carbocyclic vinyl partners. Under our standard conditions, we found that *syn*-elimination to form **25** was very slow, but upon addition of excess NaOMe (20 equiv), and warming to room temperature the desired elimination took place, cleanly affording **25** in near quantitative yield with no loss of enantiomeric purity. These conditions could also be employed for the synthesis of heterocyclic substrate **26**, which was obtained in 93% yield with complete enantiospecificity. When our standard conditions were applied to the coupling of a cyclic enamine, the desired product **27** was not observed. However, using conditions we recently reported for a *syn*-selective variant of the Zweifel reaction employing PhSeCl followed by *m*-CPBA[10a] the product was obtained in 68% yield. Taking (3,6-dihydro-2H-pyran-4-yl)lithium as a representative example, coupling with several boronic esters was attempted. We found that the coupling reaction worked well with a series of secondary, primary, tertiary and aromatic boronic esters, affording the resulting products **26**, **28**–**30** in excellent yields.

We also investigated the coupling of a steroid-derived cyclopentenyl lithium. In this case, the intermediate β-iodoboronic ester was isolated cleanly, but proved resistant to NaOMe mediated *syn* elimination.[15] Fortunately, we found that addition of TBAF in THF brought about the desired elimination providing the desired alkene **31** in 69% yield (2 steps). A range of different aromatic boronic esters could also be coupled with this vinyl lithium enabling the synthesis of a series of derivatives of the anticancer agent Abiraterone (**32**–**36**).[16] Notably, in contrast to **31**, the *syn* elimination for these examples did not require addition of TBAF and could be carried out with sodium methoxide. The enhanced rate of elimination observed in these cases is likely a consequence of the benzylic nature of the β-iodoboronic ester intermediates.[17]

Scheme 4. Coupling of functionalized vinyl lithiums with boronic esters: substrate scope[a]

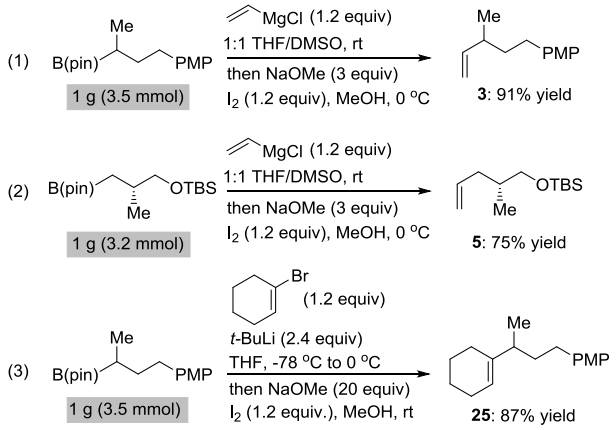


[a] Reaction conditions: boronic ester (1 equiv), vinyl lithium (0.9-2 equiv), THF, –78 °C to 0 °C, 30 min; then NaOMe (3 equiv), I_2 (1.2 equiv), THF/MeOH, 0 °C, 30 min. Vinyl lithium reagents were generated by deprotonation or by exchange with the corresponding vinyl halide or stannane (see SI for details). [b] NaOMe was not added. [c] elimination was carried out with 20 equiv of NaOMe, rt, 16 h. [d] PhSeCl followed by *m*-CPBA. [e] elimination was carried out with TBAF·3H_2O (10 equiv).

Finally, to demonstrate the utility of this method, we aimed to carry out several of the reactions on a gram scale (Scheme 5). Our newly developed conditions for coupling of vinylmagnesium chloride with boronic esters proved to be readily scalable and we could access **3** and **5** in 91% and 75% yield

respectively. Additionally, a representative coupling of a cyclic vinyl bromide conducted on a gram scale, provided **25** in 87% yield.

Scheme 5. Gram Scale Couplings



In conclusion, we have developed a robust procedure that enables the transition-metal free coupling of alkenyl magnesium and lithium reagents with boronic esters. The coupling enables commercially available vinyl Grignard reagents to be used in Zweifel-type coupling reactions for the first time. Additionally, we have shown that a wide range of substituted cyclic and acyclic alkenyl partners can be employed in the coupling, thus greatly expanding the synthetic potential of the procedure. We believe that this process will serve as a useful transition-metal-free alternative to the Suzuki–Miyaura cross-coupling for the synthesis of both chiral and achiral alkene products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

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Author Contributions

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ACKNOWLEDGMENT

We thank EPSRC (EP/I038071/1) and Bristol University for financial support. W.N. thanks the Development and Promotion of Science and Technology (DPST) Thailand for a PhD studentship. We are grateful to Dr Yunfei Luo (Hefei University of Technology) for providing us with a sample of a steroidal vinyl iodide. We thank Prof. Tim Gallagher (Bristol University) and Dr Eddie L. Myers (Bristol University) for helpful discussions.

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(17) With aromatic migrating groups, an alternative pathway involving protodeboronation followed by E2 elimination is conceivable although we have not observed any deborylated intermediates.